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Hydroxyurea Use During Pregnancy: A Case Report in Sickle Cell Disease and Review of the Literature

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A patient being treated for sickle cell disease with hydroxyurea (1 g/d) conceived, and drug treatment was discontinued at nine weeks gestational age. The pregnancy and delivery were complicated by vaso-oclusive crises. A healthy male infant was born at 39 weeks with no evidence of congenital malformations. A literature review, including this case, suggests that the risk of hydroxyurea exposure during in pregnancy may have been overestimated. Further studies are required to determine its safety in pregnancy. Am. J. Hematol. 60:148–150, 1999. © 1999 Wiley-Liss, Inc.

Key words: hydroxyurea; sickle cell disease; pregnancy

INTRODUCTION

Hydroxyurea (HU) is an antineoplastic agent used for various indications in hematology and oncology. The precise mechanism by which HU produces its cytotoxic effects is still obscure. The use of antineoplastic agents during pregnancy represents a difficult problem due to their teratogenic potential. HU is a potent teratogen in all animal species yet tested and qualifies as a universal teratogen [1]. HU produced defects of the central nervous system, palate, and skeleton in pregnant rats injected with 185 to 1,000 mg/kg on gestational day 9, 10, 11, or 12 [2]. Neural tube and heart defects were induced in hamsters given intravenous HU at 50 mg on day 9, 10, or 11 [3]. Teratogenicity was also demonstrated in cats when administered orally in a single daily dose of 50 or 100 mg/kg from gestation days 10 to 20 [4]. HU administered intravenously to pregnant rhesus monkeys at a cumulative dose greater than 500 mg/kg between days 21 and 44 induced multiple skeletal, genitourinary, cardiac, and ocular anomalies [5]. A literature review based on a Medline (1966–1998) search combining HU and pregnancy, revealed clinical reports on 15 women exposed to the drug during pregnancy (Table I). It seems that the risk of teratogenicity in humans may have been overestimated. Normal pregnancy outcomes have been reported in women who took HU, and there have been no reports of teratogenesis or mutagenesis in humans. Since 50% of pregnancies are unplanned [17] and may result in inadvertent fetal drug exposure, it is important to pool experiences and data on HU administration, especially in the first trimester of pregnancy. We report another case of HU exposure in pregnancy, when administered for sickle cell disease (SCD), with an apparently successful outcome.

CASE REPORT

A 22-year-old G1P0 black woman presented in the Motherisk Clinic in September 1995 at 11 weeks gestational age for concerns regarding HU exposure in pregnancy. Her past medical history was significant for SCD for which she had been treated with a 1 g daily dose of HU in conjunction with 5 mg folic acid daily since 1992. The patient's hematological data, while on HU, around her last menstrual period were hemoglobin (Hb) 93 g/L, mean corpuscular volume (MCV) 110, Hb S 83.1%, Hb F 14%. She had discontinued the HU at 9 weeks gestational age upon pregnancy confirmation. After receiving counseling concerning the potential risk of HU to the fetus, the possibility of obstetric complications due to

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TABLE I. Summary of Published Literature on HU Exposure During Pregnancy*

Article	# Women	Indication	Dose	Exp. time	Outcome
Doney et al. 1979 [6]	2	AML	1:8 g iv	1:2nd trimester	1:TA in 2nd trimester, phenotypically normal male
			2.8 g iv	2:3rd trimester	2:NVD healthy premature male, 2.13 kg
Patel et al. 1991 [7]	1	CML	0.5–1 g/d	Throughout	NVD 36 weeks male, 2.67 kg, normal, F/U 26 months
Tertian et al. 1992 [8]	1	CML	1–3 g/d	0–37 weeks	C/S 38 weeks male, 310 kg normal, F/U 32 months
Delmier et al. 1992 [9]		CML	1.5 g/d	Throughout	1:eclampsia 26 weeks stillborn male, normal phenotype 2:NVD 40 weeks male, 3.20 kg, normal
Jackson et al. 1993 [10]	1	CML	0.5–3 g/d	Throughout	IUGR, mild pre-eclampsia at 35 weeks, NVD 37 weeks, female, 2.85 kg, normal, F/U 5 months
Fitzgerald and McCann 1993 [11]	1	CML	N/A	0–2 weeks + 2nd + 3rd trimester	C/S normal male 3.40 kg F/U < 1 year
Szanto and Kovacs 1993 [12]	1	CML	1.5–2.5 g/d	Throughout	NVD at term, female, 3.44 kg, normal F/U 6 weeks
Cinkotai et al. 1994 [13]	1	ET	1–2 g/d	0–6 weeks	C/S 35 weeks male, 3.10 kg normal, F/U 32 months
Fernandez 1994 [14]	1	ET	N/A	N/A	TA 21 weeks due to maternal complications
Dell'Isola et al. 1997 [15]	1	ET	0.5–1 g/d	18–28 weeks	C/S 37 weeks male, 2.97 kg, normal
Charache et al. 1995 [16]	3	SCD	N/A	1st trimester	2 TAs, 1 NVD fullterm

*HU, hydroxyurea; NVD, normal vaginal delivery; C/S, cesarian section; TA, therapeutic abortion; F/U, follow up; AML, acute myelogenous leukemia; CML, chronic myeloid leukaemia; ET, essentaial thrombocythemia; IUGR, intra uterine growth restriction; N/A, not available; i/v, intravenous

SCD, and about the disease prognosis, as well as genetic counseling, she decided to continue with the pregnancy. The father was tested and found to be Hb C trait. The first trimester was complicated by a urinary tract infection treated with antibiotics for 1 week. By the end of the first trimester the patient had an Hb of 88 g/L, MCV 88, Hb S 83.3%, and Hb F 14.5%. Serial ultrasound scans were performed throughout the pregnancy to monitor fetal well being. A level II ultrasound did not show any congenital anomalies. At seven months gestation, she was hospitalization for a vaso-occlusive crisis, during which she developed anemia with an Hb of 62 g/L, requiring RBC transfusion. Ceftriaxone and erythromycin coverage was initiated for possible pneumonia and she was treated with oxygen and intramuscular meperidine 50 mg q 6 hr as needed for the crisis until induction of vaginal delivery at 39 weeks gestation. A live male infant weighing 3.24 kg was delivered with Apgar scores of 8 at 1 min and 10 at 5 min. His length was 55 cm and head circumference, 31 cm. Full physical examination of the neonate was unremarkable. The neonate was monitored in the NICU for 4 days for opioid withdrawal symptoms which he did not develop. There were no perinatal complications. He was tested at 1 year of age by HPLC analysis and found to be a compound heterozygote for Hb S and Hb C with a slightly elevated Hb F (Hb S 43.5%, Hb C 45.6%, Hb F 5.8%, Hb A_2 5.1%). Up to the age of 15 months, the infant's development has been normal.

During delivery, the mother had another vaso-occlusive crisis. She stayed in hospital for one week and was treated with oxygen and morphine. The crisis resolved 10 days after discharge.

DISCUSSION

SCD poses considerable risks for both the woman and her infant in pregnancy [18]. An extensive review comparing maternal and perinatal outcomes from before and after 1972, reported a decline of maternal mortality from 6% to 1% in these two periods [19]. A recently published report on maternal and fetal outcomes of pregnancy in women with SCD provided data on 320 pregnancies to 155 women with SCD. Nonsickle related antepartum and intrapartum complications were comparable with those of African American women who did not have SCD. Rates of maternal morbidity from SCD were the same during pregnancy as during the nonpregnant state [20].

SCD affects women of childbearing age. It is a challenge to the practitioner, with few therapeutic options for prophylaxis. HU has recently been shown to decrease the frequency of painful crises in SCD [16]. The potential beneficial effects of HU in SCD probably result from an increase in the synthesis of Hb F.

Generally, cytotoxic agents given during the first trimester of pregnancy are associated with a significant increase in the incidence of fetal malformations as well as with miscarriages. In a review on chemotherapy-induced teratogenesis [21] the apparent rate of fetal malformations from first-trimester exposure to combination chemotherapy was only slightly higher than that ob-

served with single-agent therapy: 25% of 24 cases vs. 17% of 139 cases, respectively. If one excludes the folate antagonists and those cases involving concomitant use of radiotherapy, however, the incidence for single agents declines to 6%. Table I summarizes the published literature to date on HU in pregnancy, based on a Medline search. In the nine cases in which first-trimester exposure was documented, no malformations were reported. Second- and third-trimester exposure did not demonstrate any fetal toxic effects (e.g., myelosuppression). Although the number of cases reported is too small to establish the safety of HU during pregnancy, it suggests that the potential of fetal adverse effects with HU is not very high. Further studies will be needed before a consensus is made on new therapeutic approaches in young women with SCD. Until then, these case reports may be valuable for the individual patient with SCD who had first trimester exposure to HU before making a decision on the fate of her pregnancy. Theoretical concern exists, however, regarding potential carcinogenesis and mutagenesis in long-term use of this agent.

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